THE SYNTHESIS AND CHARACTERIZATION OF NEW COPPER COORDINATION COMPLEXES CONTAINING AN ASYMMETRIC COORDINATING CHELATE LIGAND: APPLICATION TO ENZYME ACTIVE SITE MODELING *

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ABSTRACT

A new class of ligand which produces a binuclear metal complex with coordination asymmetry has been designed and synthesized. A binuclear copper complex has been prepared and characterized including a single crystal x-ray structure analysis. The structure reveals that one copper is 5-coordinate (distorted square pyramidal) while the other copper is only 4-coordinate (distorted square planar) and are separated by an endogenous μ-alkoxo oxygen and a bridging acetate. Although this structural type of chelator has been found in biological systems, it has not been previously described for inorganic coordination complexes prepared by design. It is anticipated that this ligand and derivatives of it will play an important role in mimicking chemical reactivity of enzyme active sites that function by substrate interaction at only one metal of a multimetal active site.

INTRODUCTION

The catalytic oxidation of light hydrocarbons, especially methane derived from natural gas, is an important research area attracting considerable attention. The potential for natural gas (methane) processing will depend on the development of catalyzed routes directly converting methane to higher valued products (heavier hydrocarbons, olefins, and alcohols). However, methane is chemically quite inert and has not proved easy to convert to liquid hydrocarbons. As a result, no technologies are currently available to process methane economically. It is well-known that a select group of aerobic soil/water bacteria called methanotrophs can efficiently and

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selectively utilize methane as the sole source of their energy and carbon for cellular growth.[1] The first reaction in this metabolic pathway is catalyzed by the enzyme methane monooxygenase (MMO) forming methanol:

$$CH_4 + O_2 + NADH + H^+ \xrightarrow[\text{MMO}]{25\text{-}50\ ^\circ C} CH_3OH + H_2O + NAD^+$$

Methanol is a technologically important product from this partial oxidation of methane since it can be easily converted to liquid hydrocarbon transportation fuels, used directly as a liquid fuel itself, or serve as a feedstock for fine chemicals production.

Microorganisms can produce MMO in two distinct forms: a membrane-bound particulate form or a discrete soluble form. The soluble form consist of three main proteins: A, B, and C. Protein A is an iron-containing oxygenase that reacts with methane, producing methanol,[2] and is therefore the focus of our work. Spectroscopic and thermodynamic studies have postulated that the metals in Protein A occur in a binuclear iron center and function as the active site for methane oxidation.[3,4,5] Although some of the details vary, the general description of the iron site in Protein A is a binuclear cluster containing some type of μ-oxo ligand between the iron atoms. The remaining ligands (derived from adjacent amino acid residues) coordinate to the metals through nitrogen or oxygen and the Fe-Fe distance is between 3.0-3.5 Å. Compared to the soluble form of MMO the particulate form is poorly characterized and is thought to contain copper ions at the active site. This form is also active in methane oxidation in the biological system.[6]

Our work centers on the synthesis and characterization of inorganic/organic chemical models of the active site of MMO (both particulate and soluble). We have focused on the synthesis of an unsymmetrical, binuclear chelating ligand possessing an alkoxo group that can serve as a bridging μ-oxo ligand. The advantage of such a ligand system is twofold: (a) metal complexes of an asymmetric binucleating ligand will provide coordinative unsaturation at only one metal resulting in focused substrate reactivity at that site and (b) a single ligand with binuclear coordination provides a more robust environment for metal oxidation state changes and accompanying chemical reactivity.

We report here the synthesis of a prototype asymmetrical binuclear chelating ligand, its reactivity with copper ion, and characterization of two new copper chelate complexes. This work provides the first proof-of-concept for the formation of a binuclear complex with different coordination at each metal ion. Such complexes are relevant to the development of model systems for the active site of MMO.

EXPERIMENTAL

The synthesis of the chelating ligand HMeL obtained by a five step procedure in ~35% overall yield is outlined in scheme 1. The synthesis of copper complexes of this ligand are described below.

(N,N,N'-tris-((N-methyl)-2-benzoimidazolylmethyl)-N'-methyl-1,3-diamino-2-proprionato) copper(II) perchlorate [CuHMeL](ClO4)2·CH3CN (**1**). A solution of 1.00g (1.86 mmol) of HMeL in 15 mL methanol was treated with a solution of 0.688g $Cu(ClO_4)_2 \cdot xH_2O$ (17.2% Cu, 1.86 mmol Cu^{2+}) in 15 mL methanol with stirring. A blue precipitate forms immediately on addition of copper solution and the mixture was allowed to stir at room temperature for 10 minutes. The resulting mixture was cooled at -20°C for ~1 hr, the blue solid collected on a glass frit (pale green filtrate), washed with 10-15 ml cold methanol and dried under vacuum at 25°C. Crude yield was 1.3256g of blue-green solid. The dried solid was dissolved in 75 mL hot acetonitrile, filtered hot, and cooled. X-ray quality crystals were obtained by vapor diffusion of ether into this solution. The blue-green crystals were collected on a frit and vacuum dried (83% yield). Anal. Calcd. for $C_{33}H_{39}Cl_2CuN_9O_9$: C, 47.18; H, 4.68; N, 15.00. Found: C, 47.07; H, 4.85; N, 14.73.

(μ-O,O'-acetato)(N,N,N'-tris ((N-methyl)-2-benzoimidazolylmethyl)-N'-methyl-1,3-diamino-2-proprionato)dicopper(II,II) bisperchlorate [Cu2MeL(OAc)](ClO4)2·2H2O (**2**).
(a) A solution of 1.00g of HMeL (1.86 mmol) and 0.507g sodium acetate trihydrate (3.72 mmol) in 15 mL of methanol was treated with 1.377g Cu(ClO4)2·xH2O (17.2% Cu, 3.72 mmol Cu^{2+}) in 15 mL methanol with stirring. A light blue precipitate forms initially and is quickly replaced (~30 sec) by a deep blue solid. The mixture was stirred for 30 min. at room temperature and then cooled at -20°C overnight. The solid was collected on a glass frit, washed with 10mL of cold methanol, and air dried to yield 1.703g of sky-blue powder. Further purification was achieved by vapor diffusion of ether into 50 mL of an acetonitrile solution of this solid to yield dark blue crystals (90.3% yield). Anal. Calcd. for $C_{33}H_{42}Cl_2Cu_2N_8O_{13}$: C, 41.43; H, 4.64; N, 11.71. Found: C, 41.34; H, 4.64; N, 11.13. (b) A 0.1036g (0.125 mmol) sample of (**1**) was placed in 10 mL of methanol to produce a pale blue-green solution and solid. To this suspension 0.046g of $CuClO_4 \cdot xH_2O$ (0.125 mmol) followed by 0.034g sodium acetate trihydrate (0.25 mmol) were added sequentially as solids. The mixture was warmed to 50°C and stirred for 30 minutes. The solid was collected and washed with cold methanol, and recrystallized by vapor diffusion of ether in acetonitrile to yield dark blue crystals of (**2**).

RESULTS AND DISCUSSION

Scheme 1 shows the synthetic route for the prototype binuclear chelating ligand, HMeL. Elemental analysis and NMR studies confirm the composition and structure of the ligand. It possesses a hydroxy functionality that could serve as a bridging alkoxo group and aliphatic and aromatic nitrogen coordination groups (benzimidazole). Using the C-OH bond as a bisecting line in this molecule, it is clear that the ligand has the potential to coordinate two metal ions in different environments. One half of the ligand provides three coordination sites (2 nitrogens and 1 bridging oxygen) while the other half provides four coordination sites (3 nitrogens and 1 bridging oxygen).

Reactions with copper ion demonstrate that the ligand is a potent chelating agent. Blue or blue-green colored complexes are formed rapidly in the presence of copper(II). The complexes are synthesized by stoichiometric reactions in methanol using hydrated metal salts. Characterization by elemental analysis and single crystal x-ray crystallography show that either mononuclear or binuclear complexes are obtained. For a metal-to-ligand ratio of 1:1 a mononuclear complex is obtained (Figure 1). The structure of the complex shows a distorted, trigonal bipyramidal coordination environment around Cu with five Cu-N bonds (average Cu-N distance ~ 2 Å). In this case, the hydroxo functionality does not coordinate to the metal and in the structure is located remote from the metal. On the other hand, with a metal-to-ligand ratio of 2:1 and in the presence of 2 equivalents of sodium acetate, a binuclear complex is formed (Figure 2). The structure shows that the ligand has chelated two copper ions, that the copper ions share the alkoxo oxygen (bridging μ-oxo), and that a coordinated acetate ion bridges the two metals. As a result, one Cu ion is coordinatively saturated (5-coordinate distorted trigonal pyramidal) while the other Cu is only four coordinate (distorted square pyramid). The mixed oxygen, nitrogen ligation have average Cu-N(O) distances of ~2 Å typical of Cu(II) coordination complexes. The role of acetate in this reaction is both to serve as a coordinating bridge between the two copper sites and as a general base that assists in deprotonation of the organic hydroxo group forming the charged alkoxo bridging species. Interestingly, the crystal structure shows that in the solid-state an oxygen from one of the ClO_4^- counterions is weakly bound to the 4-coordinate Cu ion (about 2.6 Å away) suggesting that this Cu is coordinatively unsaturated and that there is a potential 5th site for binding. Initial attempts to demonstrate this binding site have been successful and an azido bridged binuclear Cu complex has been prepared and isolated.[7] It appears that complexes of this type can show selective reactivity at one metal site. Such behavior is a key requirement for bioinorganic mimics of the MMO active site.

CONCLUSIONS

A binuclear, unsymmetric coordinating ligand that is an effective metal chelator has been designed and prepared. The new ligand has been shown to react rapidly with copper(II) forming a variety of copper coordination complexes. The binuclear complex is of significant interest since it represents proof-of-principle for the development of coordinatively asymmetric, binuclear metal chelate complexes. Although this structural type of chelator now appears to be common in biological systems, it has not been previously described for inorganic coordination chemistry. It is expected that this ligand and derivatives of it will play an important role in the development of bioinorganic complexes that aim to mimic enzyme active sites that function by substrate interaction at only one metal site of a multimetal active site.

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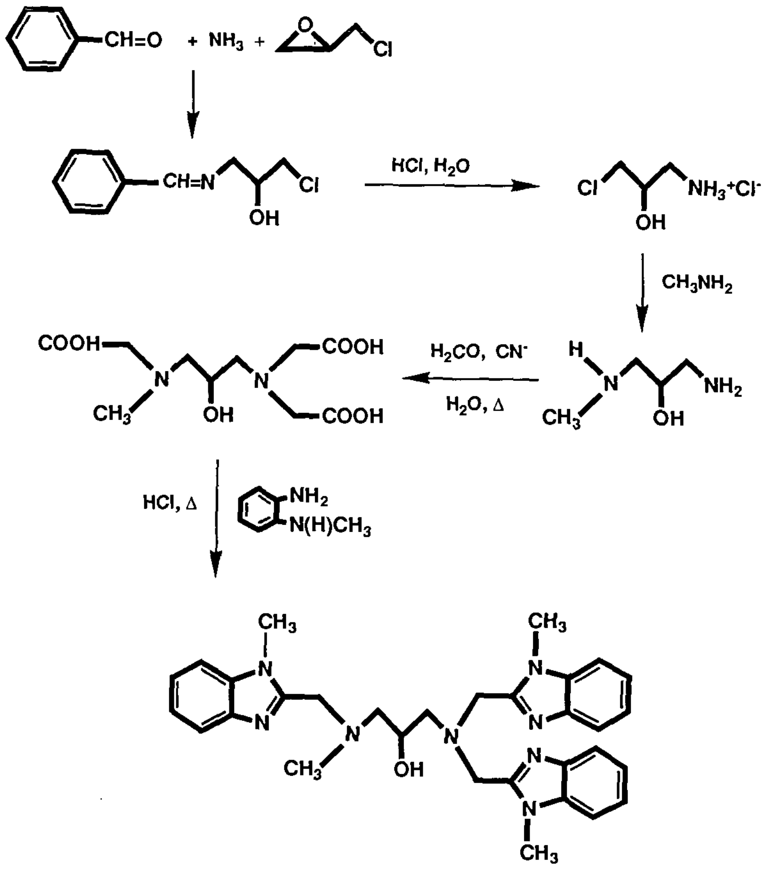

Scheme 1. Reaction pathway producing chelating ligand [HMeL].

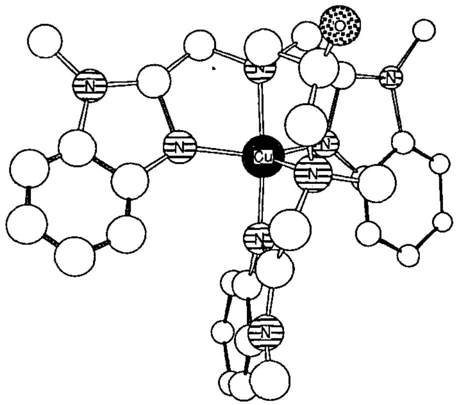

Figure 1. Structure of mononuclear Cu(II) complex (**1**). Open circles represent carbon atoms. Hydrogen atoms not shown for clarity.

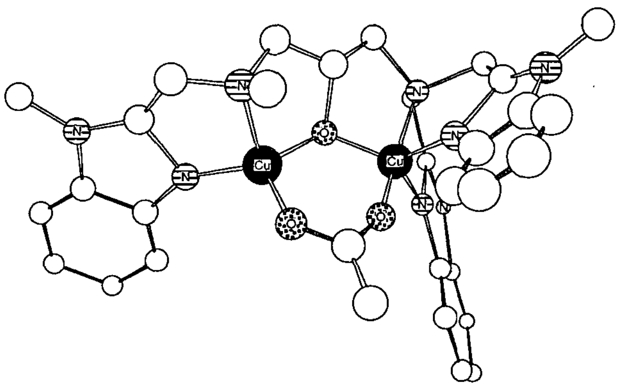

Figure 2. Structure of binuclear Cu(II) complex (**2**). Open circles represent carbon atoms. Hydrogen atoms not shown for clarity.